Original Communications

Histoplasmosis: Clinical Syndromes and Management

Joseph M. Stinson, MD, Paul A. Talley, MD, and Frank E. Thomas, MD
Nashville, Tennessee

The fungus Histoplasma capsulatum produces a spectrum of disease forms ranging from a benign self-limited illness to progressive disseminated disease with a 50 percent mortality rate. The drug of choice, amphotericin B, must be given intravenously over a prolonged course and carries a high incidence of toxicity. Thus, optimal managment of serious forms of histoplasmosis requires considerable clinical judgment.

Definition

Histoplasmosis is an infectious granulomatous disease caused by the dimorphic fungus Histoplasma capsulatum. The fungus exists in a mycelial form in soil and in a yeast form at body temperature. The presence of fowl excreta in the soil acts as a nutrient to fungal growth, and large numbers of infecting spores may become airborne in sites such as chicken houses, hollow trees, caves, attics, farm silos, under pigeon roosts, and places in which large numbers of fowl or bats congregate or have congregated. Bats may be actually infected, whereas fowl are not infected because of their high body temperature.[1] Extensive epidemiological studies have identified the endemic region as the Mississippi—Ohio River Valley and Central Atlantic States.[2] Over 90 percent of the healthy young adult population in Middle Tennessee, Kentucky, Arkansas, and Missouri may have positive histoplasmin skin tests, which renders such tests useless for diagnosing active disease in these areas.[2] Epidemics of histoplasmosis are also known to occur outside the endemic area.[3] The disease may be classified as acute, chronic, and disseminated histoplasmosis.[4] In addition, complications of the disease are often considered a fourth class.[1]

From the Divisions of Pulmonary and Infectious Diseases, Department of Internal Medicine, Meharry Medical College. Requests for reprints should be addressed to Dr. Joseph M. Stinson, Division of Pulmonary Diseases, Meharry Medical College, Nashville, TN 37208.

Acute Histoplasmosis

The majority of persons infected with H capsulatum remain asymptomatic and evidence of infection is found by positive skin tests or residual roentgenographic changes. The latter consist of a Ghon complex in the lung similar to that resulting from primary infection of tuberculosis (Figure 1), and often calcifications in the spleen and liver, indicating benign dissemination during the primary infection.[5] Negative skin tests do not necessarily indicate that a subject has not had histoplasmosis, as in endemic areas cutaneous reactivity may disappear with time only to return later.

Heavier exposures to the infecting organisms produce an influenza-like syndrome with fever, chills, cough, malaise, and generalized aching sensations. The chest x-ray usually shows patchy pneumonic infiltrates varying from a few to diffuse involvement. Lesions may appear as multiple nodules and heal, usually without specific therapy, as typical "buckshot calcifications" throughout the lung parenchyma. This is the form of histoplasmosis occurring in epidemics and is more likely to occur outside or on the fringes of endemic areas where patients have not previously had the asymptomatic infection described above. Within the endemic area where heavy inocula of infective spores produce a reinfection stage of the disease, symptoms are usually milder but the chest film may be more like that of miliary tuberculosis. In either case the disease is usually self-limiting, although progression to disseminated histoplasmosis or acute respiratory failure is possible.[5]

Chronic Histoplasmosis

Chronic disease appears to be lung-specific and is usually called chronic pulmonary histoplasmosis.[6,7] It is in practically every respect like tuberculosis. There is a predilection for the apical and posterior segments of upper lobes of the lung; cavity formation is frequent (Figure 2); and lesions heal by contraction. On a background of centrilobular or bullous emphysema, the basic roentgenographic lesions are an interstitial pneumonitis, often with very dense areas of focal necrosis with streaking from the lesions toward the lung hila representing distended lym-

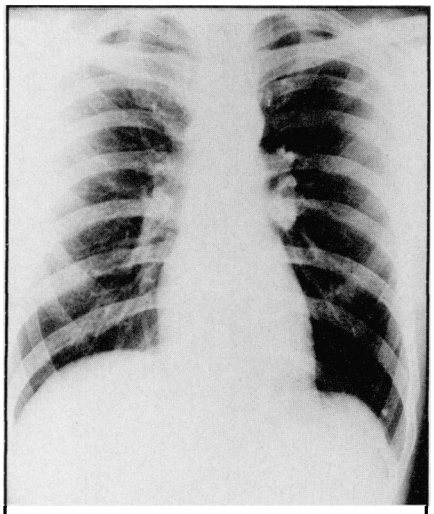

Figure 1. Chest roentgenogram of an 18-year-old black male, showing left hilar adenopathy with calcific change. This patient also had calcifications in the region of the spleen on abdominal films. Healed primary histoplasmosis

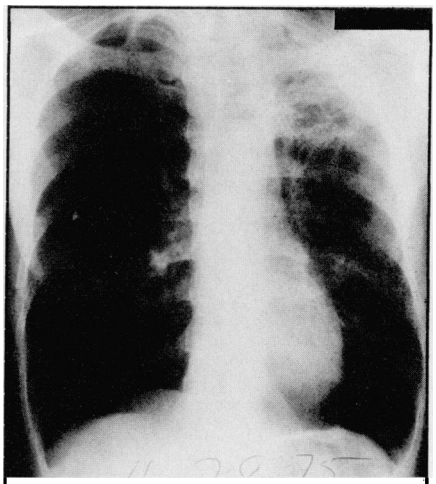

Figure 2. 54-year-old white male with dyspnea and productive cough. Pneumonic lesions with cavities in left upper lobe, emphysema. Chronic pulmonary histoplasmosis

phatics.[7] Patients usually have only mild degrees of illness, with a nonproductive cough and weight loss as the most prevalent symptoms. Other clinical findings include sputum production, vague chest pain, dyspnea, fever, night sweats, and hemoptysis. Chronic pulmonary histoplasmosis seems to represent exogenous reinfection as opposed to endogenous reactivation in the similar stage of tuberculosis.[6]

Disseminated Histoplasmosis

Progressive disseminated histoplasmosis is a rare form of the disease occurring in less than one percent of patients with disease.[5,8] The significance of this form of the disease lies in the 50 percent mortality rate, even with specific therapy.[5,8,9] Progressive dissemination occurs primarily in the compromised host, eg, very young children, immunosuppressed patients, those with lymphomas, etc. Pulmonary involvement is not prominent although hazy, usually stable interstitial infiltrates may be appreciated on the chest film. There may be significant involvement of the heart,[10] central nervous system,[11] mucosal surfaces,[4,8] and other organ systems.[5,8,9] All patients with disseminated disease must be assessed frequently for evidence of adrenal insufficiency, since this is the most common cause of death.[12]

Complications

Complications of histoplasmosis represent largely progressive healing or arrested primary complex. The histoplasmoma is the most common of these, and is responsible for over half of the "solitary pulmonary nodules" seen in endemic areas.[13] A peripheral lesion, the histoplasmoma rarely compresses vital structures and is important primarily because it is necessary to distinguish it from neoplasms. Smooth, well-defined borders are helpful in this regard, and even more significance may be attached to the finding of central or lamellar calcification in the lesion. The histoplasmoma may enlarge by progressive deposition of collagen in the periphery, apparently secondary to continued release of antigen from a scant number of organisms in the necrotic center.

A similar lesion may persist in the mediastinum (Figure 3), and progressive enlargement encroaches upon important mediastinal structures such as bronchi, pulmonary arteries and veins, superior vena cava, and esophagus.[14,15] These supposed arrested lesions therefore have the potential for becoming life-threatening. Similarly, involved peribronchial lymph nodes may erode bronchi leading to broncholithiasis and occasionally massive pulmonary hemorrhage.[15] Residual pulmonary cavities may be invaded by Aspergillus fumigatus in the form of fungus balls, and thick-walled cavities have potential for enlargement with progressive destruction of lung tissue, the so-called marching cavities.[7]

Diagnosis

Diagnostic measures are listed in Table 1 in order of decreasing significance. Definitive diagnosis requires culture of H capsulatum from sputum or biopsy specimens on blood agar, Subaroud agar, or brain-heart infusion agar. Growth of the organisms is often difficult, especially in laboratories in which few such studies are performed. Demonstration of the organisms on sputum smears or biopsy specimens stained with Wright or methanamine silver stains is also usually acceptable evidence of active disease.[7] Histoplasmin complement fixation titers must be 1:64 or greater to be considered diagnostic.[7] There may, however, be cross-reaction with other fungi such as blastomyces, and false positive serologies are known to occur in other disorders as well.[16] Goodwin and associates[7] have described the roentgenologic picture in chronic pulmonary histoplasmosis which may provide strong suggestive evidence of the disease.

In the endemic area the histoplasmin skin test is useful primarily as a test for anergy. With regard to diag-

nosis of disease, a positive skin test is most significant if a simultaneous tuberculin skin test is negative. When diagnosis is the object, blood for complement-fixation studies must be drawn prior to the skin test, as the latter may lead to positive serology. In desseminated disease, bone marrow and blood cultures may be positive for the causative organisms.[9]

Therapy

The only currently recommended specific drug therapy for histoplasmosis is with amphotericin B (Fungizone). This fungistatic agent is toxic (Table 2) and must be administered intravenously over a long period of time. Its use is therefore usually limited to life-threatening or organ-threatening disease.

Acute histoplasmosis usually requires only symptomatic therapy,[5] and specific therapy is generally of no value for complications of the primary complex.[15] Specific drug therapy is essential for meaningful survival in disseminated disease.[8,9,12] This leaves the chronic pulmonary form of the disease for careful consideration. The early stage of chronic pulmonary disease (pneumonic lesions and early cavitation) may be effectively managed with modified bed rest.[17] Persistent cavities and progressive pulmonary disease should be treated.

Amphotericin B is given empirically to a total dose of 2 gm. Beginning with 1 or 5 mg in 100–500 cc of 5 percent dextrose in water, the daily dose is gradually increased to 25-35 mg daily over a four to six hour period. Solution in saline may lead to precipitation.[18] In severe progressive disease, several smaller doses may be given on the first day of therapy to more rapidly reach the optimal daily dose.[19] An alternate method of administering amphotericin B is based on maintaining a blood level of 1.56 μg/ml (twice the minimal inhibitory capacity) where such determinations are available. This supposedly reduces the incidence of toxicity.[20] In either case, the total dose requires approximately ten weeks.

Table 2 lists common complications of amphotericin B therapy.[19] Superficial thrombophlebitis at the site of infusion may be minimized by regularly alternating the site and by adding 5,000 units of heparin to each infusion. Chills and fever, nausea and vomiting, and headache and myalgia are managed by premedication with antipyretics, antiemetics, Benadryl, and/or mineralocorticosteroids. Hypokalemia is related to a distal type of renal tubular acidosis, and may require oral potassium supplementation. Amphotericin B interferes with bone marrow iron utilization and regularly leads to anemia, usually not requiring therapy. Some degree of azotemia almost always develops. Elevation of blood urea nitrogen to 40 mg/100 ml or more is indication for temporary interruption of the drug for a few days, after which therapy should be resumed at the small initial dose and again gradually increased to the therapeutic level.

Pulmonary cavities persisting in spite of adequate amphotericin B, especially if they are thick-walled, may require surgical excision.[21]

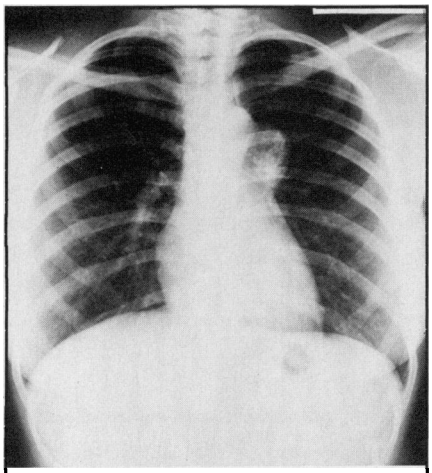

Figure 3. Chest film in an asymptomatic 30-year-old black female. Mass with calcium just below level of aortic arch. Fibrosing mediastinitis

Table 1. Diagnostic Measures
Sputum Culture
Sputum Smear
Histology
Serology
Chest X-Ray
Skin Test

Table 2. Complications of Amphotericin B
Local Thrombophlebitis
Chills and Fever
Nausea and Vomiting
Myalgia, Headache
Hypokalemia
Anemia
Azotemia

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